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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,937	03/19/2004	Bela Anand-Apte	CCF-6494NP	8141

26294 7590 03/30/2006

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,937	ANAND-APTE, BELA	
	Examiner	Art Unit	
	Rosanne Kosson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 14-21, in the reply filed on March 13, 2006 is acknowledged. Claims 1-13 and 22-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. No claims have been amended, canceled or added. Accordingly, claims 14-21 are examined on the merits herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite a method of inhibiting VEGF binding to VEGFR2 (VEGF receptor 2), comprising contacting cells (presumably cells that express VEGFR2, although this feature is not recited in the claims, a feature without which the claimed method would not work) with TIMP3 or a variant of TIMP3, wherein the variant is an analog, a derivative, a mimetic or a fragment of TIMP3. The terms variant, analog, derivative and mimetic are not defined in the specification (these words appear to be used interchangeably, see pp. 16-18), and no variants, analogs, derivatives or mimetics of TIMP3

are identified in the specification, either by name or by structure. Regarding fragments, only two fragments are identified, an N-terminal portion (amino acids 1-121) and a C-terminal portion (amino acids 122-188). Thus, no examples of variants, analogs, derivatives and mimetics of TIMP3 are provided and only two examples of fragments of TIMP3 are provided. Consequently, there is no evidence that any representative species of such large and varied genera, molecules or compounds that are variants, analogs, derivatives, mimetics and fragments of TIMP3, were in the possession of the inventors at the time of filing.

To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any variants, analogs, derivatives or mimetics of TIMP3 and discloses only two fragments of TIMP3.

Therefore, the claims fail to satisfy the written description requirement.

Claims 14-21 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting VEGF binding to VEGFR2 (VEGF receptor 2), comprising contacting cells (as noted above, presumably cells that express VEGFR2, although this feature is not recited in the claims, a feature without which the claimed method would not work) with TIMP3, does not reasonably provide enablement

for a method of inhibiting VEGF binding to VEGFR2, comprising contacting these same cells with a variant of TIMP3, wherein the variant is an analog, a derivative, a mimetic or a fragment of TIMP3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. In claiming a method using any fragment of TIMP3, these claims recite fragments that are not disclosed in the specification. The specification discloses only two fragments that are functional, i.e., amino acids 122-188 of TIMP3, the fragment that is shown in SEQ ID NO: 9, and SEQ ID NO: 2, which contains the fragment of SEQ ID NO: 9 along with some of the N-terminal portion of the molecule. Thus, the specification does not teach how to make and use fragments of the claimed whole polypeptide that block the binding of VEGF to VEGFR2. Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue

experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

The claims are very broad because they recite a method of inhibiting the binding of VEGF to VEGFR2 on cells, comprising contacting the cells with any variant of TIMP3. A variant is any analog, derivative, mimetic or fragment of TIMP3.

2. The nature of the invention.

The invention is designed to provide a method of inhibiting angiogenesis to treat a disease in which angiogenesis plays a role (such as cancer), because the binding of VEGF to VEGFR2 plays a substantial role in endothelial cell proliferation.

3. The state of prior art.

As discussed below, Qi et al., at the ARVO Annual Meeting in May 2002 (ARVO Annual Meeting Abstract Search and Program Planner, Abstract No. 2753, May 5-10, 2002) disclosed a method of inhibiting the proliferation and migration of cells expressing VEGFR2 by contacting the cells with TIMP3, which inhibited the binding of VEGF to VEGFR2.

4. The relative skill in the art.

The relative skill in the art as it relates to the claimed invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

Because it is not known how to identify, select and formulate variants, analogs, derivatives, mimetics and fragments of TIMP3 that have the same functional properties as TIMP3, in particular, the function of inhibiting the binding of VEGF to VEGFR2, the specification needs to have more detail as how to make and use the invention. Based on the prior art and the instant specification, one skilled in the art would not be able to identify suitable variants, analogs, derivatives, mimetics and fragments of TIMP3 that inhibit VEGF-VEGFR2 binding, apart from the fragment of SEQ ID NO: 9. Therefore, one of skill in the

art would not be able to formulate these variants, analogs, derivatives, mimetics and fragments of TIMP3, and, as a result, he would not be able to predict the effect of contacting cells expressing VEGFR2 with VEGF and one of these variants, analogs, derivatives, mimetics or fragments of TIMP3. One of skill in the art would have no idea whether any of these variants, analogs, derivatives, mimetics and fragments of TIMP3 would have any effect on VEGF-VEGFR2 binding, and, if there were an effect, what that effect would be- increased binding or decreased binding- and to what extent (slightly increased, greatly increased, slightly decreased, greatly decreased, etc.). Because the specification does not provide guidance for the claimed method with respect to variants, analogs, derivatives, mimetics and fragments of TIMP3, it cannot be predicted that such a method could be performed.

6. The amount of guidance present.

Applicants have not provided any guidance for variants, analogs, derivatives, mimetics and fragments of TIMP3. Guidance is provided only for the fragments of SEQ ID NO: 9 (the C-terminal portion) and SEQ ID NO: 2 (the last 24 amino acids of the N-terminal portion plus the C-terminal portion). The specification also teaches that SEQ ID NO: 1 (TIMP3) works in the claimed method.

7. The existence of working examples.

The specification does not provide any working examples in which the claimed method is practiced with a variant, analog, derivative, mimetic or fragment of TIMP3. Only TIMP3 is used.

8. The quantity of experimentation necessary.

To prove that all variants, analogs, derivatives, mimetics and fragments of TIMP3

may be used in the instant invention, many experiments would have to be conducted under a wide range of conditions. First, several large groups variants would have to be prepared and then identified as having the claimed property of inhibiting the binding of VEGF to VEGFR2. One group of molecules would have to be analogs (molecules with a very similar structure and the same functional properties), one group of molecules would have to be derivatives (chemically derivatized versions of SEQ ID NO: 1 that have the same functional properties), one group of molecules would have to be mimetics (molecules with the same functional properties and a different structure, which would have to be guessed and arrived at by random trial-and-error experimentation, absent guidance in the specification), and one group of molecules would have to be fragments (any number of amino acids deleted from SEQ ID NO: 1 at any arrangement of positions, all the molecules having the same functional properties). Each molecule in each group would have to be tested under a range of conditions (variant concentration, VEGF concentration, cell concentration, buffers, temperatures, cell types, cell source (species of cell donor, e.g., human, mouse, or rat). The data from each group of variant molecules would have to show that each variant molecule tested in each experiment is able to inhibit the binding of VEGF to VEGFR2. These types of experiments and data are missing from the specification. A great deal of guidance is needed to establish that the claimed invention may be performed with any variant, analog, derivative, mimetic or fragments of TIMP3, because the claims recite that any variant, analog, derivative, mimetic or fragment of TIMP3 may be used, although only two fragments have been disclosed. Because these variants, analogs, derivatives, mimetics and fragments of TIMP3 have not been disclosed and cannot be determined without a great deal of experimentation, they cannot be predicted. Even if one variant in

one group could be identified, and data under one set of conditions in one experiment obtained, without a very large amount of data, such a result could not be expected with a different variant, particularly a different variant in a different group (e.g., a derivative vs. an analog) in an assay under different conditions, such as a different concentration of VEGF or cells, even using cells of the same type.

In view of the foregoing, the claims fail to satisfy the enablement requirement.

Additionally, claims 14-21 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. As discussed above, claim 14 recites a method of inhibiting the binding of VEGF to VEGFR2, but the only step recited is that of contacting cells that express VEGFR1 with a composition comprising TIMP3. In order for the method to work, the cells must also express VEGFR2, and this limitation must be recited in the claims. There is no point in contacting cells that express VEGFR1 and that need not express VEGFR2 with TIMP3, which has no effect on the binding of anything to VEGFR1. This limitation that is missing from the claims is critical and essential to the practice of the invention, but is not included in the claim(s) or enabled by their disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-17 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 15 recites that TIMP3 does not "substantially"

inhibit the binding of VEGF to VEGFR1. "Substantially inhibiting" is not defined in the specification. Thus, it cannot be determined what degree of inhibition Applicant intends to claim, and the metes and bounds of the claim are unclear. Applicant may amend the claim by deleting the word "substantially." Appropriate correction is required.

Claims 16 and 17 recite that the VEGF variant is "substantially free" of the "N-terminal domain" of TIMP3 and of metalloproteinase inhibiting activity. "Substantially free" is not defined in the specification. Thus, it cannot be determined what percentage of the TIMP3 molecules have no N-terminal domain or what percentage of the TIMP3 molecules have no metalloproteinase activity. As a result, the metes and bounds of the claims are unclear. Applicant may amend the claims to delete the word "substantially." Appropriate correction is required.

Also, claim 16 recites the term "N-terminal domain of TIMP3." The specification does not indicate which portion of TIMP3 is the N-terminal domain, rendering Applicant's intended meaning unclear. Applicant may amend the claim to recite the portion of TIMP3 that he removed from the protein to produce a fragment that functional in the claimed method, i.e., either the first 120 amino acids, yielding SEQ ID NO: 2, or the first 144 amino acids, yielding SEQ ID NO: 9. Appropriate correction is required.

Claim 19 recites that the TIMP3 variant is "operatively linked" to a therapeutic agent. Operatively linked is not defined in the specification. Thus, Applicant's intended meaning is not clear. One of skill in the art would be able to link TIMP3, or the fragment of SEQ ID NOS: 2 or 9, to a therapeutic agent by chemical coupling (performing a chemical or enzymatic reaction creating a covalent bond), or he would be able to prepare a fusion protein for linking TIMP3, or the fragment of SEQ ID NOS: 2 or 9, to a protein therapeutic

agent. But, such techniques do not define "operatively linked." Applicant may amend the claim to delete the word "operatively." Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 14, 15 and 18-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Qi et al. (ARVO Annual Meeting Abstract Search and Program Planner, Abstract No. 2753, May 5-10, 2002). As noted above, Qi et al. disclose a method of inhibiting the proliferation and migration of porcine cells expressing VEGFR2 by contacting the cells with TIMP3, which inhibits the binding of VEGF to VEGFR2. Because these cells are endothelial cells, the express VEGFR1 and VEGFR2. Qi et al. indicate that only the VEGFR2 signaling pathway is disrupted. Thus, TIMP3 does not bind to VEGFR1.

Regarding claims 19 and 21, Qi et al. disclose that TIMP3 is an angiogenesis inhibitor. Thus, it is operatively linked to therapeutic agent, as it is a therapeutic agent. It is, i.a., an anti-cancer agent and an ocular anti-neovascularization agent.

Regarding claims 18 and 20, TIMP3 is a VEGF-inhibiting variant (variant being undefined, as discussed above) comprising at least a portion of SEQ ID NO: 2. Particularly if the TIMP3 is from an animal other than pig, for example, if the human gene, which is known and characterized, is introduced into the porcine cells expressing VEGFR2, this TIMP3 is a variant relative to porcine TIMP3.

In view of the foregoing, a holding of anticipation is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner, Art Unit 1653

rk/2006-03-20

Rosanne Kosson

ROBERT A. WAX
PRIMARY EXAMINER